UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: **Oct 27, 2015**

SUBJECT: Waiver Request to Register a Diflubenzuron Feed-Through Product for Swine Fly Control.

PC Code: 108201	**DP Barcode:** 425923
Decision No.: 489559	**Registration No.:** 270-379
Petition No.: NA	**Regulatory Action:** Waiver Request
Risk Assessment Type: NA	**Case No.:** 0144
TXR No.: NA	**CAS No:** 35367-38-5
MRID No.: 49509301	**40 CFR:** 180.377

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Risk Assessment Branch 4
Health Effects Division (7509P)

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Risk Assessment Branch 4, HED (7509P)
11/4/15

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Invertebrate and Vertebrate Branch 2/RD (7505P)

Waiver Request

The registrant had previously submitted a request to register a diflubenzuron (*N*-[((4-chlorophenyl)amino) carbonyl]-2,6-difluorobenzimide) feed through use on cattle, horses, and swine for fly control. HED recommended against the registration until residue data in hog manure were provided (see Appendix A, ChemSAC minutes). HED pointed out that there are no residue data pertaining to the use of hog manure (containing diflubenzuron residues) on cropland. A cattle feed-through has been registered since 1985.

HED recommended that the data be collected in a tiered approach. HED proposed dosing three hogs at the proposed rate, collecting and processing the manure in the same way as it is processed prior to field application, and analyzing the manure for diflubenzuron and its metabolites [p-chloroaniline (PCA), and p-chlorophenyl urea (CPU)]. If quantifiable residues of diflubenzuron (DFB) or its metabolites were found, the registrant would need to conduct a small-scale residue field trial program on representative crops (including at a minimum, corn and radish) and analyze the raw agricultural commodities for DFB and its metabolites.

Instead of generating the data as recommended by HED, the registrant submitted a waiver request/rationale (MRID 49509301, 351 pages) for not submitting these data. The registrant maintains that current federal and state restrictions on the use of manure as a fertilizer, i.e., to prevent nitrogen/phosphorus (N/P (as P_2O_5)) runoff from the treated land, would limit the amount of total manure applied, and there would be no residues in the crops grown in soil treated with the swine manure.

Registration Division asked BEAD to review specific parts of the waiver and BEAD's review, Diflubenzuron Residues in Swine Manure and applied Crop (email to RD, 6/24/2015), is included in Appendix B. BEAD was able to assess the accuracy of the calculations and state regulations and has provided additional usage information for swine manure on crops in the United States.

This waiver request was presented to ChemSAC on Oct 7, 2015. The waiver memo and waiver request were both approved.

Conclusions/Residues Resulting From Application of "Treated" Swine Manure to Crop Land

Based on the nursery farm specialty, the application rate for diflubenzuron would be ca. 11.9 g/acre or 0.03 lb diflubenzuron/acre based on phosphorous plant needs, 0.05 lbs ai/A based on total nitrogen plant needs.

Approximately 10-20% of administered diflubenzuron dose is eliminated in the urine as metabolites, while 80-90% of the administered dose is excreted in the feces as diflubenzuron (goat/swine studies). Using the upper bound estimate of 20%, then PCA levels would be ca. 3% (i.e., 20% x 17%) of the administered dose (0.06 mg/gal or ca 0.003 lbs/A), DFBA levels would be ca. 11% (55% x 20%) of the administered dose (0.21 mg/gal or 0.01 lb/A), and CPU levels would be ca. 2% (20% x 10%) of the administered dose (0.04 mg/gal or 0.02 lbs/A).

The application rates for diflubenzuron and its metabolites in manure is much lower than in the available crop rotation/field accumulation studies (conducted at 0.375 lb ai/A/season). It is also much lower the seasonal crop application rate for agricultural crop, which can be up to 1.0 lb ai/season (tree nuts). No detectable residues of diflubenzuron or its metabolites are expected in rotated crops as a result of using swine feed-through swine manure on cropland as a fertilizer. The application of the manure would reflect application of the parent and metabolites, not just the parent compound; however, the longer crop rotation intervals do reflect breakdown of the parent compound and would adequately represent application of parent/metabolites.

EFED has determined that this new registration would not increase the estimated drinking water numbers; therefore, a new risk assessment is not required. EFED also agree with the estimated equivalent application rate for diflubenzuron of ca. 0.03-0.05 lb ai/A. BEAD also concurs with the calculation of the effective use rate from applying the "treated" swine manure.

Background

Diflubenzuron (DFB) is an insecticide/acaricide that acts as a chitin inhibitor to suppress the growth of many leaf-eating larvae, mosquito larvae, aquatic midges, rust mite, boll weevil, and flies. Permanent tolerances are established for residues of the insecticide diflubenzuron in or on fat and meat of cattle, goats, hogs, horses, and sheep at 0.05 ppm; milk at 0.05 ppm; poultry fat, meat at 0.05 ppm; and eggs at 0.05 ppm [40 CFR 180.377(a)(1)]. Tolerances are established for also established for residues of the insecticide diflubenzuron, in or on cattle meat byproducts (mbyp), goat mbyp, hog mbyp, horse mbyp, and sheep mbyp at 0.15 ppm. The tolerance for all mbyp and many raw agricultural commodities [40 CFR 180.377(a)(2)] is determined by measuring the sum of diflubenzuron (N-[[(4-chloro phenyl)amino]carbonyl]-2,6-difluorobenzamide), 4-chlorophenyl urea (CPU) and 4-chloroaniline (PCA), calculated as the stoichiometric equivalent of diflubenzuron.

Rat metabolism data indicate that diflubenzuron does not metabolize to PCA or CPU nor is CPU converted to PCA. The HED Metabolism Assessment Review Committee (MARC) met several times (02/20/2001 and 05/8/2001), concurred with the study findings, and concluded that a 2% *in vivo* conversion factor for diflubenzuron to PCA or CPU should be dropped (MARC memo, 05/31/2001). Based on the toxicity observed only at higher doses in the NTP studies for both CPU and PCA, additional CPU and PCA toxicity data are not needed. The toxicity of CPA and PCA will be considered equal to diflubenzuron for the non-cancer risk assessment. The MARC recommended that non-carcinogenic risk assessment include parent, CPU and PCA. Therefore, HED is concerned with accounting for the presence of these three metabolites which could potentially be transfered to agricultural crops when the manure is applied to agricultural land. HED previously determined that 4-chloroacetanilide (PCAA) is neither an animal nor plant metabolite of diflubenzuron.

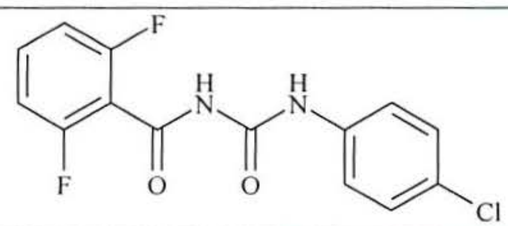
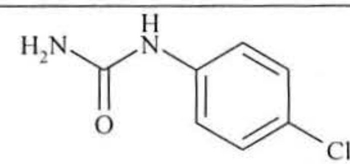
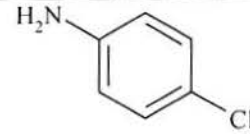
Table.1. Diflubenzuron Nomenclature.	
Compound	
Common Name	Diflubenzuron
Trade and other Names	Dimilin, Vigilante, Micromite, Adept
IUPAC Name	1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl)urea
CAS Name	*N*-[[(4-chlorophenyl)amino]carbonyl]-2,6-difluorobenzamide
CAS Registry Number	35367-38-5

Table.1. Diflubenzuron Nomenclature.	
Regulated Metabolite	
Common name	4-chlorophenylurea (CPU)
Regulated Metabolite	
Common Name	4-chloroaniline (PCA)

Use Directions

The registrant is proposing diflubenzuron as a feed-through pesticide for administration to hogs for the control of flies in manure. There are already feed-through products registered for cattle and horses. Table 2 provides the use directions for the feed-through use of diflubenzuron to control flies in cattle, horse and swine manure.

Table 2. Use Directions for the Feed-Through Use to Control Flies in Manure.		
Species	**Daily Feeding Rate of Diflubenzuron (DFB)**	
	mg/kg	**mg/cwt**
Cattle (existing use)	0.10	4.55
Horses (existing use)	0.15	6.82
Swine	**0.20-0.30**	**9.10 - 13.64**

The most recent drinking water residues were provided by the Environmental Fate and Effects Division, summarized in the following memorandum: "Ecological Risk and Drinking Water Assessments for Proposed Label Amendments of Diflubenzuron." (DP #423330, F. Khan, 04/20/2015)

Swine manure from large production hog farms is generally handled in two main types of storage facilities, lagoons, and pits that may be flushed into ponds or tanks. Manure from the animals normally drops through slats in the floor and is diluted by wash water and further diluted by pit-recharge water and flush water as it passes through the system to the processing or storage area. Lagoons are designed to facilitate sediment deposition and anaerobic metabolism of the manure, while storage ponds are not designed for either sediment deposition or anaerobic metabolism.

A storage pond may appear the same as a lagoon. They are not typically designed to operate in an anaerobic treatment mode as are lagoons. Storage ponds are much smaller, and reportedly the potential for odor is greater than for a lagoon system. Manure storages are sized to store the manure, waterer wastage, and washdown water for a defined storage period. Land application plans can include winter and summer crops as well as forest land.

Swine manure, from all types of treatment and storage facilities is applied to crop land as fertilizer. The application rates being determined by the nitrogen/phosphorous (N/P) content of the manure and the nutrient requirements of the crop that will be planted at that location.

The concentration of DFB in the manure that will be spread on cropland intended for corn planting (which is typical, the corn then is fed to the hogs) can be calculated.

Total DFB (finishing) 0.2 mg/kg * 454 kg hog = 90.8 mg/454 kg, or 90.8 mg per 1,000 lbs hog (Note: 1,000 lbs is an animal unit (AU)).

Total DFB (nursery) 0.3 mg/kg * 454 kg hog = 136.1 mg/454 kg, or 136.1 mg per 1,000 lbs hog

The amount of diflubenzuron in manure from lagoons or storage ponds can be estimated based on the amount of diflubenzuron administered per animal weight and the volume of diluted manure produced based on animal weight. According to Clemson University, the volume of manure plus rinse water produced per day per 1,000 lbs. live weight of feeder-to-finishing hogs is 1.62 cubic feet/day, or 12.118 gallons/1,000 lbs/day. The volume of pit-recharge manure produced per day per 1,000 lbs weight/day for feeder-to-finishing hogs is 6.8 cubic feet/day, or 50.86 gallons/1,000 lbs/day. The concentration of DFB and its metabolites combined in the recharge dilution of the manure is equal to the administered dose in mg/1,000 lbs./day divided by the volume of pit-recharge manure or ((90.8 mg/1,000 lbs/day) ÷ 50.99 gal), i.e., 1.78 mg/gallon. The table below shows the DFB concentration in recharge diluted manure for the five different types of farm specialties: 1) farrow-to-wean, 2) nursery, 3) farrow-to-feeder, 4) feeder-to-finish, 5) farrow-to-finish.

90.8 mg/1,000 lbs. ÷ 50.9* gallons/1,000 lbs/day = 1.784 mg/gal/1,000 lbs animal weight (*volume of pit recharge per day per 1,000 lbs bw/day, for feeder-to-finisher).

Table 3. Manure Volume/Day for Different Farm Types.

Farm Type	Manure & Waste Water (gallons/AU/day)	Pit Recharge (gallons/AU/day)	DFB Recharge Concentration (mg/gallon)
Fallow to Wean	8.68	69.6	1.304
Nursery	12.12	70.3	1.935*
Fallow-to-Finish	9.28	70.3	1.290
Feeder-to-Finish	12.12	50.9	1.784
Farrow-to-finish	11.15	58.3	1.555

*The DFB recharge concentration for nursery reflects use on much smaller animals, and smaller operations.

Once the concentration of DFB in recharged diluted manure is established, estimates of diflubenzuron in different types of manure handling systems can be estimated based on the dilution of manure in the different types of systems. The amount of nitrogen (N) from flush and pit-recharge buildings was identified in sampled South Caroline farms as ca. 17.0 lbs/1,000 gallons. This nitrogen level was compared with the total nitrogen level in lagoon water, which was 4.8 lb/1,000 gallons, a dilution factor of 3.54 lower. If phosphorous (as P_2O_5) is used to compare the dilution of the pit-recharge (13.4 lbs/1,000 gal) and lagoon water (2.8 lbs/1,000 gal), the dilution factor is higher, 4.79. The registrant applied the lower dilution factor to the diflubenzuron concentration in the recharge manure to estimate the diflubenzuron concentration in lagoon water.

In a similar way, the total nitrogen was used to estimate the diflubenzuron concentration in manure storage pond water. The total nitrogen in storage pond surface water was 6.3 lb/1,000 gal, a factor of 2.7 lower than in the pit-recharge manure (17.0 lbs/1,000 gal). The table below presents the registrant calculated concentrations for DFB in lagoon and storage pond water based on the dilution of the nitrogen (N) concentration.

Table 4. Diflubenzuron (DFB) Concentrations in Swine Lagoon and Pond Storage Water.

Farm Type	DFB Recharge Conc. (mg/1,000 gal)	DFB Lagoon Dilution 3.54 (N dilution) (mg/1,000 gal)	DFB Pond Dilution 2.7 (N dilution) (mg/1,000 gal)	DFB Agitated Solids Dilution 2.125 (N dilution) (mg/1,000 gal)
Fallow to Wean	1304	368.4	483.0	613.7
Nursery	1935	547.7	716.8	910.8
Fallow-to-Finish	1290	364.5	477.9	607.2
Feeder-to-Finish	1784	503.8	660.6	839.2
Farrow-to-finish	1555	439.2	575.9	731.7

Appling Manure to Cropland

According to the registrant, state and local regulations control the amount of manure that can be applied to crops based on the nutrient content of the manure. Nitrogen and phosphorus content of the manure is variable depending on the storage and treatment of the manure. Total nitrogen in swine lagoons is ca. 4.8 lbs/1,000 gal of manure and total nitrogen in the lagoon sludge is estimated to be 21.6 lbs/1,000 gal of manure. The phosphorus in the lagoon surface water is estimated to be 2.8 lbs/1,000 gal, and the phosphorous in the lagoon sludge is estimated to be 47.3 lbs/1,000 gal of manure.

The registrant has provided N/P worksheets (Purdue 1999) providing estimates of the nitrogen and phosphorus that are appropriate to support crop growth for corn (see Appendix B, corn is largest single crop treated). The worksheets indicate that the corn crop is expected to yield 160 bushels/acre. The nitrogen needed to support that growth is 190 lb/acre, and the phosphorus application needed is 60 lb/acre (P_2O_5).

The more dilute lagoon and pond water provide the worst-case estimates of diflubenzuron applied because as the manure is more concentrated, the nutrients increase to high levels that severely restrict the amount of manure that can be applied to crop land. Assuming that the manure lagoon water containing the diflubenzuron also contains 4.24 lbs of plant available nitrogen (i.e., NH_4^+ + (0.6 (an empirical factor) * organic nitrogen); when applied by direct injection, and 2.8 lb phosphorus (P_2O_5).

Manure applied based on nitrogen (190 lb/acre)/(4.24 lbs/1,000 gal) = 44.81 * 1,000 gal/acre

Manure applied based on phosphorus (60 lb/acre)/(2.8 lbs/1,000 gal) = 21.43 * 1,000 gal/acre

The amount of diflubenzuron applied, based on these nutrient application levels, would be:

Feeder-to-finish DFB based on nitrogen = 504 mg/1,000 gal * 44.81 * 1,000 gal = 22.6 g/acre

Feeder-to-finish DFB based on phosphorous = 504 mg/1,000 gal * 21.43 * 1,000 gal = 10.8 g/acre

Table 5. Diflubenzuron (DFB) Applied to Corn Fields.

	Lagoon Surface Water (P_2O_5 Based)		**Agitated Water and Solids (P_2O_5 Based)**		**Pond Water and Solids (P_2O_5 Based)**	
Farm Type	**Appln. vol/acre @ 60 lbs P_2O_5/acre (* 1,000 gal)**	**DFB applied based on P_2O_5 (g/acre)**	**Appln. vol/acre @ 60 lbs P_2O_5/acre (* 1,000 gal)**	**DFB applied based on P_2O_5 (g/acre)**	**Appln. vol/acre @ 60 lbs P_2O_5/acre (* 1,000 gal)**	**DFB applied based on P_2O_5 (g/acre)**
Fallow-to-Wean	21.43	7.9	5.31	3.3	16.67	8.0
Nursery	21.43	11.7	5.31	4.8	16.67	***11.9***
Fallow-to-Finish	21.43	7.8	5.31	3.2	16.67	8.0
Feeder-to-Finish	21.43	10.8	5.31	4.5	16.67	11.0
Farrow-to-finish	21.43	9.4	5.31	3.9	16.67	9.6

Based on the nursery farm specialty (and P_20_5 loading), the application of diflubenzuron would be 11.9 g/acre or 0.03 lb diflubenzuron/acre. If the applications were made based on total nitrogen, the application rate would be ca. 0.05 lbs ai/A.

Metabolism

Cattle/Goat

The nature of the residue in animals is adequately understood based on acceptable poultry, ruminant, and swine metabolism studies. Terminal residues identified in animal tissues, milk, and eggs include diflubenzuron, 2-hydroxydiflubenzuron (2HDFB), 2,6-difluorobenzamide (DFBAM), 2,6-difluorobenzoic acid (DFBA), 4-chlorophenyl urea (CPU), and 4-chloroaniline (PCA).

In one ruminant metabolism study, dairy cows were dosed orally via capsule for up to 28 days with double ring-labeled ^{14}C-diflubenzuron at rates equivalent to 0.05, 0.5, and 5 ppm in the diet. At the 0.05 and 0.5 ppm dose levels, radioactive residues, expressed in diflubenzuron equivalents, were nondetectable (<0.00014 - <0.0003) in milk. At the 5 ppm dose level (ca 0.07 mg/kg dose, 0.3x), radioactive residues in milk plateaued after 4 days and were 0.0063-0.0134 ppm. After 28 days of dosing, radioactive residues in muscle, fat, and kidney were nondetectable at the 0.05 ppm (<0.007 ppm), 0.5 ppm (<0.034 ppm), and 5 ppm (<0.04 ppm) dose levels. Radioactive residues in liver were 0.0071 ppm at the 0.05 ppm level, 0.0708 ppm at the 0.5 ppm level, and 0.54 ppm at the 5 ppm level.

In the same study, an additional cow was dosed with ^{14}C-diflubenzuron at 250 ppm (ca. 18 mg/kg or 18X) for 8 consecutive days and sacrificed. Extraction and TLC analysis of liver residues isolated diflubenzuron (3.0% TRR), PCA (1.2% TRR), CPU (0.15% TRR), and 2,6-difluorobenzoic acid (DFBA) (10.9% TRR). Although milk from the same animal was not completely characterized, it was determined that parent was not present in the milk.

In the subsequent ruminant metabolism study, which the Agency concluded is adequate, four lactating goats were dosed orally via capsule for 3 consecutive days with double ring-labeled [14C]diflubenzuron. Two goats were dosed at a rate equivalent to ca. 10 ppm in the diet and two at a rate equivalent to ca. 250 ppm.

Radioactive residues in the feces and urine accounted for approximately 88% of the administered dose for both the low and high dose goats. After 3 days of dosing, TRRs in the low dose (ca. 10 ppm) goats were 0.007-0.009 ppm in milk, 0.217-0.262 ppm in liver, 0.016-0.019 ppm in kidney, 0.001 ppm in muscle, and 0.004 ppm in fat; and TRRs in the high dose (250 ppm) goats were 0.22 ppm in milk, 3.24-6.06 ppm in liver, 0.36-1.02 ppm in kidney, 0.02-0.05 ppm in muscle, and 0.12-0.30 ppm in fat. Radioactive residues were characterized in milk and liver. Extraction of milk released 85% of the TRR. The principal residues identified consisted of CPU (29-55% TRR) and 2,6-difluorobenzamide (DFBAM, 6-8% TRR). PCA was nondetectable (<0.001 ppm) in milk from both low and high dose goats.

Extraction of liver released 90% of the TRR. The principal residues identified consisted of diflubenzuron (7% TRR), 2-hydroxydiflubenzuron (7% TRR), CPU (16% TRR), and DFBAM (1% TRR). PCA was not detected in liver from the low dose goats, but accounted for approximately 0.4% of the TRR (0.011-0.028 ppm) in liver of the high dose goats.

Conclusions: PCA is a very minor metabolite, while CPU is a major metabolite.

Swine

A Poland-China Duroc female weighing 46 kg was given a capsule a single dose of 5 mg/k (16.7X) of ^{14}C–diflubenzuron (labeled in both rings). Urine and feces were collected at 12-hour intervals until sacrifice after 11 days. Samples of liver, kidney, fat, muscle, skin, and bone were taken for ^{14}C measurement by combustion and LCS. Feces were extracted with ethyl acetate and urine samples was extracted with diethyl ether. Metabolites were characterized using TLC and HPLC with reference compounds CPU (p-chlorophenyl urea), PCA (p-chloroanaline), DFBA (2,6-difluorobenzoic acid), 2-OH-DFB, and 3-OH-DFB.

In the course of the 11 days after treatment, 82% of the administered radioactive dose was excreted in the feces, and ca. 5% was recovered in the urine. 78% of the administered dose was recovered by day 4. The highest residue was 0.3 ppm in the fat. In feces, all radioactive materials were identified as diflubenzuron.

Table 6. Radioactivity in Pig Tissues, 11 days after dosing with 5 mg/kg bw.

Sample	mg/kg Diflubenzuron Equivalents
Omental fat	0.30
Subcutaneous fat	0.20
Liver	0.23
Kidney	0.11
Longissimus dorsi muscle	0.050
Latissimus dorsi muscle	0.042

Identification of metabolites in the urine revealed CPU, DFBA, PCA, and DFBAM. The data indicate that the absorbed diflubenzuron is metabolized in the pig; however, the bulk of the dose is eliminated in the feces as the parent compound.

Table 7. Quantification and TLC Characterization of Metabolites in Pig Urine.

Compound	Percent of Dose	Percent of TRR in Urine
Diflubenzuron	0.45	7.5
Unknown	0.68	11
Unknown	1.5	25
PCA (p-chloroanaline)	**1.0**	17
DFBAM (2,6-diflurobenzamide)	0.83	14
CPU (p-chlorophenyl urea)	0.82	14
Unknown	0.31	5.2
DFBA (2,6-difluorobenzoic acid)	0.29	4.8
Origin	0.10	1.7

In the urine, only 1-2% was the parent compound. The main metabolites were formed by cleavage of the urea bridge. PCA and CPU were significant metabolites in the urine, but minor metabolites when viewed as a percentage of the administered dose.

Multi-Dose Study

In a different study, five females and four castrated male pigs (Landrece) weighing between 20 and 23 kg were dosed by capsule with ^{14}C-diflurobenzuron twice a day for 10.5 days. Each dose was 7.5 mg. As the pigs were fed 1 kg dry feed per day, this represented a daily intake of 15 mg/kg bw/day on the first day decreasing to 0.48-0.58 mg/kg bw/day on day 10, as the pigs gained weight. Urine and feces were collected every 24 hours throughout the dosing period and the 7-day withdrawal period for 4 of the pigs. The pigs were slaughtered in three groups of three, one group just following the final dose, another seven days after the final dose, and the last group 14 days after the final dose.

The total excretion was 88-92% of the administered dose, of which 69-79% was in the feces and 8.6% - 10% in the urine. The highest residue levels were in the liver. Only the results of the pigs sacrificed after the last dose are presented, since the draft label does not have a withdrawal period.

Table 8. Radioactivity in Pig Tissue 6 Hours after the Last Dose (mg/kg as Diflubenzuron).	
Skeletal muscle, fore	0.009
Hind	0.011
Fat: renal	0.017
Subcutaneous	0.011
Omental	0.009
Liver	0.11
Kidney	0.062

In the feces, almost all the radioactivity was unchanged parent compound. In urine, only 1-2% was parent compound. The main metabolites reflected cleavage of the urea bridge. **PCA was not identified in the urine from this study.**

Table 9. Diflubenzuron and Metabolites in Pig liver, Kidney, Feces, and Urine (% of the TRR).

Compound	Liver	Kidney	Feces	Urine
Diflubenzuron			99	1
DFBA (2,6-difluorobenzoic acid)	30	55		**55**
DFHA (glycine conjugate of DFBA)	20	10		20
DFBAM (2,6-diflurobenzamide)				5
CPU (p-chlorophenyl urea)				**10**
Unknown extractables	50	35	1	5

Conclusions: Total excretion of the administered dose was ca. 90%, with ca. 80% in the feces (all parent compound) and 10% in the urine. Only one percent of the urinary analytes were the parent compound diflubenzuron. In the 11-day swine study, 1.0% of the administered dose was

PCA in urine, 0.29% of the administered dose was DFBA in urine, and 0.8% of the administered dose was CPU in urine.

The amount of parent and the metabolites that enter the manure of feeder-to-finish hogs can be estimated. In short, 80% of the administered dose will be the parent compound. The maximum of 1.9 x 80% is ca. 1.5 mg/gal of the parent compound DFB. PCA levels would be ca. 0.019 mg/gal (i.e., 1% x 1.9 mg/gal), DFBA levels would be ca. 0.006 mg/gal, and CPU levels would be ca. 0.015 mg/gal.

Livestock Feeding Studies

There are ruminant and/or poultry feed items associated with the current uses of diflubenzuron. The most recent maximum theoretical dietary burden (MTDBs) of diflubenzuron are 22.2 ppm for beef cattle, 34.8 ppm for dairy cattle, and 0.058 ppm for hog. This is considered to be a very conservative estimate.

Livestock Feeding Studies

Residue Chemistry Chapter of the Diflubenzuron Registration Standard (11/84)
Residue Chemistry Chapter of the Diflubenzuron RED (DP# 209032, S. Knizner, 3/15/1995)

Numerous diflubenzuron feeding studies have been reviewed previously by HED. Those that are the most relevant to the current petitions are discussed.

In one cattle study, lactating cows were dosed orally twice a day with diflubenzuron at either 25 ppm (10X, based on 600 kg bw cow dosed at 0.1 mg/kg bw consuming 24 kg feed) or 250 (100X) ppm in the diet for up to 28 consecutive days. Residues of diflubenzuron *per se* were nondetectable (<0.05 ppm) in milk from both feeding levels sampled following 1 to 28 days of dosing. Residues of diflubenzuron *per se* were also nondetectable (<0.05 ppm) in the fat, muscle, liver, and kidneys of cows sacrificed after 8, 18, and 28 days of dosing at 25 ppm (10X). For cows sacrificed after dosing at 250 ppm for 8, 18 and 28 days, residues of diflubenzuron were nondetectable (<0.05 ppm) in the muscle and kidney, 0.06-0.08 ppm in fat, and 0.09-0.1 ppm in liver.

In the third study, four dairy calves were fed diflubenzuron at a rate of 2.8 mg ai/kg body weight (28X) for 4-5 months and two were sacrificed. Then three others were fed at 1 mg ai/kg body (10X) weight for another year and sacrificed. The 2.8 and 1.0 mg/kg doses were equivalent to approximately 180 ppm and 65 ppm, respectively, in the diet. Following dosing at the high dose, residues of diflubenzuron were 0.02 ppm in liver and kidney, 0.04-0.08 ppm in fat, and <0.02 ppm in muscle. Residues of diflubenzuron were nondetectable (<0.02 ppm) in tissues from livestock after dosing at the low dose.

Residue data are also available to support the use of the 9.7% diflubenzuron bolus in beef and dairy cattle. In this study, dairy and beef cattle were each treated once with two 50 gram boluses of 10% diflubenzuron (2X the label rate). This dose was calculated to be equivalent to approximately 8 ppm in the diet. Diflubenzuron residues were non-detectable (less than 0.04 ppm) in milk collected 20, 30 and 60 days after treatment. In tissue samples collected 32, 62 and 99 days after treatment, diflubenzuron residues were non-detectable (less than 0.04 ppm) in muscle and kidney, from less than 0.04 to 0.06 ppm in fat, and from less than 0.04 to 0.07 ppm in liver.

Conclusions. HED concludes that the current tolerances on meat and milk are adequate to cover the added residues resulting from the proposed feed through use, which is essentially equivalent to uses already registered for cattle (beef and dairy) and horses. A feed through use on poultry is not being proposed.

Plant/Fungi Uptake of Diflubenzuron

The qualitative nature of the residue in plants is adequately understood based on data from citrus, mushroom, rice and soybean metabolism studies. In the mushroom metabolism study, compost was spawned with mushroom culture and then was treated with DFB at 1x (4/22/87, CBTS #2085). Residues of diflubenzuron (DFB), 4-chlorophenylurea (CPU), difluorobenzoic acid (DFBA), and 4-chloroaniline (p-chloroaniline, PCA) were detected at levels up to 0.18, 0.60, 4.0, and 0.02 ppm respectively.

The vast majority of the residue in citrus fruit is composed of unchanged parent compound, and no detectable levels (<1 ppb) of PCA, CPU, or DFBA were present (S. Knizner, 3/16/95).

In the soybean metabolism study, >90% of the TRR in soybean leaves was unchanged parent (ppm levels not provided). DFBA, CPU, and PCA were not detected, but the limit of detection (LOD) for these compounds was not provided. In soybean hulls, 81.4% to 97.9% of the TRR (6.57 -17.5 ppm) was identified as unchanged parent. Again, DFBA, CPU, and PCA were not detected. The LOD for these compounds was 0.3 ppm. Residues in soybean seeds were too low to allow for metabolite characterization (<0.1 to 0.038 ppm) (Memo S. Knizner, 3/16/95).

The major component of the TRR in rice straw was the parent DFB (42% of the TRR, 3.77 ppm) (Memo G. Kramer, 6/23/98; D240107). CPU, as the free metabolite, comprised 28.6% of the TRR, its conjugated form in soluble form accounted for 2.5%, and CPU bound to insolubles accounted for ~10%. In rice grain, DFB accounted for 0.3% of the TRR (0.002 ppm). The major metabolite in grain was CPU present in its free form (~20% of the TRR, 0.132 ppm). DFB in rice is metabolized via cleavage of the urea linkage to CPU and DFBA (2,6-difluorobenzoic acid); only very small concentrations of PCA are formed. The metabolism of DFB in rice grain is similar to that in cotton and citrus, and the radioactive components are also similar to those found in soil.

Conclusions: Available data indicate that DFB is degraded to DFBA and CPU in soil and water. Crops that grow on treated soil (mushrooms) or in flooded fields (rice) may have these residues in higher amounts. The crop rotation studies are more relevant to the application of manure to agricultural land. These studies are discussed below.

Crop Rotation Studies

In the confined rotational crop study, ^{14}C-diflubenzuron was applied to a sandy loam soil at a rate equivalent to 1 lb ai/A (swine manure application rate is ca. 0.03 – 0.05 lb ai/A). The soil was aged in a greenhouse for approximately 1, 4, and 12 months prior to planting radish, spinach, and wheat as representative rotational crops. The total radioactive residues in the rotational crops were highest in commodities from the 1-month plant-back interval (PBI) and declined steadily at each increasing PBI interval.

Radioactive residues in raw agricultural commodities (RACs) from the 1-month PBI were highest in radish tops (0.636 ppm) and lowest in spinach and wheat grain (about 0.06 ppm). In RACs from the 12-month PBI, ^{14}C-residues were less than 0.02 ppm in spinach, radish roots and tops, and wheat forage, and ranged from less than 0.039 to less than 0.104 ppm in wheat straw, grain, and hulls.

The principle ^{14}C-residues identified in spinach were diflubenzuron and CPU, which together accounted for 31.2% of the TRR (0.019 ppm) in spinach from the 1-month PBI and 35.3% of the TRR (0.012 ppm) in spinach from the 4-month PBI. Minor amounts (about 3% TRR) of DFBA were also detected in spinach.

In radish, the principle ^{14}C-residue isolated was CPU, accounting for 54.1% and 35.5% of the TRR in tops from the 1- and 4-month PBIs, respectively, and 21.9 and 8.6% of the TRR in roots from the 1- and 4-month PBIs, respectively. Minor amounts of diflubenzuron (less than 2% TRR) and DFBA (4-6% TRR) were also isolated.

In wheat forage from the 1- and 4-month PBIs, only minor amounts (less than 5% TRR and less than 0.01 ppm) of diflubenzuron, DFBA, and CPU were detected, although 50-62% of the TRR was solvent extractable. In addition, approximately 64% of the TRR remained unextracted from wheat straw from the 1- and 4-month PBIs. Of the ^{14}C-residues extracted from wheat straw (36% TRR), the major metabolites identified were DFBA (11-17% TRR) and CPU (7-17% TRR). ^{14}C-Residues in wheat grain and hulls were not characterized.

Field Accumulation in Rotational Crops

Uniroyal has submitted data (MRID 44689703) depicting diflubenzuron residues in representative rotational crops from two limited field trials. The available data indicated that tolerances for diflubenzuron residues in rotational crops were not required provided the Dimilin labels specify a restriction for the planting of rotation crops of at least 30 days. The rotational field trials were conducted on sandy loam soils in Madera, CA and Bernard, TX. At the CA test site, a single control plot and two treated plots were separately established for each PBI, for a total of 7 control plots and 14 treated plots. At the TX test site, one large control plot and two large treated plots were established; these large plots were each subdivided into 7 subplots, one for each PBI. Cotton was planted as the primary crop at both test sites as it has the highest labeled use rate for diflubenzuron of any rotated crop (0.375 lb ai/A/season).

Residues of diflubenzuron, CPU, and PCA were determined in the treated and control samples using adequate GC/ECD or GC/MS methods. An analytical sample set consisted of the single control sample, two fortified control samples, and the four treated samples from a given PBI at each test site. Low level residues of diflubenzuron and CPU in rotational crops were detected in the crops. Residues of PCA were <LOQ (<5 ppb) in all rotational crop commodities.

At each test site, the single control and duplicate treated subplots were planted with lettuce, turnips, and wheat as representative rotational crops at PBIs of approximately 30, 45, 60, 90, 120, 180, and 365 days after the final application of diflubenzuron.

With some exceptions, a single control and four treated samples (two treated samples/plot) of the various RACs for each crop were harvested from each PBI at each test site. Lettuce samples were harvested at maturity 81-153 days after planting (DAP). Turnips were also harvested at maturity (81-153 DAP) and separated into roots and tops. Wheat forage was sampled at 49-62 DAP. Wheat hay was harvested at the early milk or dough stage (78-237 DAP) and was air dried for 4 to 7 days prior to sampling. Wheat grain and straw samples were collected at maturity (128-269 DAP).

In lettuce, residues of diflubenzuron were <0.01 ppm except in two out of four samples from the 45-day PBI in CA, which had residues of 0.01 and 0.02 ppm. Residues of CPU were also <0.01 ppm in all samples except for two samples from the 90-day PBI in CA, which had residues of 0.01 and 0.02 ppm. Apparent residues of both diflubenzuron and CPU were <LOQ in all control samples of lettuce.

Residues of diflubenzuron were <0.01 ppm in turnip roots and tops, except in one sample of tops from CA (180-day PBI). Apparent residues of diflubenzuron were also <LOQ in all control samples. In turnip tops, residues of CPU were detected at 0.01-0.03 ppm in all treated samples from the 30- through the 180-day PBIs in CA and from the 60- and 90-day PBIs in TX. However, the control samples associated with these samples also had apparent residues of CPU at the same levels (0.01-0.03 ppm). A similar situation was noted in turnip roots. Residues of CPU were detected at 0.01-0.04 ppm in treated samples from the 30- through 120-day PBIs in CA and at 0.01-0.06 ppm in samples from the 30- and 60-day PBIs in TX. Seven out of the 12 turnip root controls had apparent residues of CPU at 0.01-0.03 ppm. Although the method recovery data for CPU in turnips indicates that an LOQ of 0.01 ppm is acceptable for roots and tops, the apparent residues of CPU in these control samples suggests that the LOQ for CPU should be at least 0.03 ppm.

In wheat forage, residues of diflubenzuron were detected at 0.01 ppm in three samples from the 90-day PBI in CA, in two samples from the 120-day PBI in CA, and in one sample each from the 365-day PBI in CA and the 180-day PBI in TX. However, apparent residues of diflubenzuron at 0.01 ppm were also detected in the three control samples from CA that were associated with these treated samples. With one exception, diflubenzuron residues in the remaining 29 forage samples were <0.01 ppm. Residues of CPU were detected at 0.01-0.02 ppm in 10 forage samples from the 30- through 90-day PBIs from CA. Residues of CPU were not detected in forage samples from TX; however, forage samples from the 30- through 120-day PBIs were unavailable from the TX test site. Apparent residues of CPU were <LOQ in all control samples of forage.

In wheat hay, residues of diflubenzuron and CPU were <0.01 ppm in all treated samples, and apparent residues of diflubenzuron were <LOQ in all control samples except for one control sample from TX with apparent residues of diflubenzuron at 0.01 ppm.

In wheat grain, diflubenzuron was detected at 0.01 ppm in one sample from CA at the 180-day PBI and in the four samples from the 45-day PBI in TX; however, the 45-day PBI control sample from TX also had apparent residues of diflubenzuron at 0.01 ppm. Diflubenzuron was <0.01 ppm in the remaining 32 treated grain samples. One sample from the 30-day PBI in CA had residues of CPU at 0.02 ppm; CPU residues were <0.01 ppm in the remaining 35 grain samples. Apparent residues of CPU were <LOQ in all control samples of grain.

Diflubenzuron was detected at 0.01 ppm in 10 wheat straw samples from various PBI in CA and from the 30-day PBI in TX; however, with one exception, the six control samples associated with these treated samples also had apparent residues of diflubenzuron at 0.01 ppm. Diflubenzuron was <0.01 ppm in the remaining 32 treated straw samples. One straw sample from the 45-day PBI in TX had residues of CPU at 0.02 ppm; CPU residues were <0.01 ppm in the remaining 41 straw samples. Apparent residues of CPU were <LOQ in all control samples of straw.

Conclusions: In lettuce, residues of diflubenzuron were <0.01 ppm except in two out of four samples from the 45-day PBI in CA, which had residues of 0.01 and **0.02 ppm**. All other commodities had residues <0.01 ppm.

Residues of CPU were detected at 0.01-0.04 ppm in treated turnip roots and tops, from the 30- through 120-day PBIs in CA and at 0.01-**0.06 ppm** in samples from the 30- and 60-day PBIs in TX. Seven out of the 12 turnip root controls had apparent residues of CPU at 0.01-0.03 ppm. Although the method recovery data for CPU in turnips indicates that an LOQ of 0.01 ppm is acceptable for roots and tops, the apparent residues of CPU in these control samples suggests that the LOQ for CPU should be at least 0.03 ppm. Most residue in the other crop had residues <0.01 ppm, or between 0.01 ppm and 0.03 ppm.

Note: The registrant also cited a JMPR reviewed studies that involved foliar spot treating with radiolabel diflubenzuron (^{14}C-chloroaniline moiety and ^{3}H-diflurobenzyl moiety) at 0.27 lbs ai/A. Samples of leaves and stems of corn were collected and analyzed for radioactivity 5 and 9 weeks after planting (15 and 19 weeks after soil treatment). Corn cobs and leaves were analyzed at harvest, 16 weeks after planting, (26 weeks after treatment). All corn cobs and leaf samples tested at harvest were below the LOQ for all residues (total TRR LOQ = 0.06 mg/kg). This study also supports the conclusion that finite residues would not be expected from the land application of the swine manure.

The JMPR review also includes data for cabbage, soybeans and apples. The leaves received spot foliar treatment in a greenhouse. No significant degradation or translocation occurred on the leaves of soybean (<0.02 mg/kg) or cabbage up to 16 weeks after application, but some may have occurred in apple leaves. Residues in apple fruit were <0.005 mg/kg 16-21 weeks after application, and no residues of CPU or PCA were detected.

Drinking Water

The most recent drinking water residues were provided by the Environmental Fate and Effects Division, summarized in the following memorandum: "Ecological Risk and Drinking Water Assessments for Proposed Label Amendments of Diflubenzuron." (DP #423330, F. Khan, 04/20/2015). EFED (F. Khan) stated in a Sept 21 email that: The maximum diflubenzuron annual application rate for citrus (0.94 lbs/A) is approximately 19X higher than the estimated application rate of 0.05lbs/A of diflubenzuron from swine manure. Therefore, EFED does not expect recently recommended EDWCs (DP 423330; April 20, 2015) for diflubenzuron and it's degradate, CPU for the citrus use to be exceeded by swine manure application to crop land.

In that review, the maximum application rate of 0.312 lbs a.i./A X 3 applications/year for citrus as well as 0.25 lbs a.i./A X 4 applications/year for tree nut were modeled with the SWCC and PRZM-GW models.

For groundwater sources of drinking water, the maximum acute and chronic estimated concentrations of CPU in shallow groundwater from PRZM-GW model for applications to citrus were 8.62 µg /L and 8.02 µg /L, respectively. However, the concentrations of diflubenzuron in groundwater were negligible. Recommended surface water and groundwater EDWCs for human health are listed in Table 10.

Table 10. Drinking Water Exposure Estimates for Diflubenzuron and its Major Degradate, CPU for Use on Various Crops.

Source	**Residue**	**Peak Exposure (µg /L)**	**Annual Mean Exposure (µg /L)**	**30-year Average Exposure (µg/L)**
Surface water[1]	Diflubenzuron[2]	4.61	0.41	0.38
	CPU[2]	6.83	0.89	0.51
	Total	11.44	1.3	0.89
Groundwater[1]	Diflubenzuron	0	---	0
	CPU	8.62	---	8.02
	Total	8.62	0	8.02

[1] EDWCs generated using SWCC and PRZM-GW models for aerial LV application of 0.312 lbs a.i./A X 3 applications for citrus use [2] Estimated in FL Citrus scenario

Environmental Fate

Diflubenzuron appears to be relatively non-persistent and immobile under normal use conditions. The major route of dissipation appears to be biotic processes (half-life of approximately 2 days for aerobic soil metabolism). Diflubenzuron is stable to hydrolysis and photolysis.

Anaerobic aquatic metabolism: The half-life of 34 days for diflubenzuron when applied to silt loam soil and incubated at 24C under anaerobic conditions is 34 days. The study identified three degradates: 2,6-difluorobenzoic acid, 4-chlorophenyl urea, and 4-chloroaniline.

Conclusions/Residues Resulting From Application of Treated Swine Manure to Crop Land

Based on the nursery farm specialty, the application of diflubenzuron would be 11.9 g/acre or ca. 0.03 lb diflubenzuron/acre based on plant phosphorus requirements (0.05 lb ai/A based on total N requirements).

Assuming 20% of administered diflubenzuron dose is eliminated in the urine, which seems reasonable based on the studies available. Then PCA levels would be ca. 3% (i.e., 20% x 17%) of the administered dose (0.06 mg/gal or ca 0.003 lbs/A), DFBA levels would be ca. 11% (55% x 20%) of the administered dose (0.21 mg/gal or 0.01 lb/A), and CPU levels would be ca. 2% (20% x 10%) of the administered dose (0.04 mg/gal or 0.02 lbs/A).

The application rates for diflubenzuron and its metabolites in manure are much lower than in the available crop rotation/field accumulation studies (0.375 lb ai/A/season) where below the LOQ or in a few cases, very low residues were detected. In those cases, the control samples also reflected residues at these same low levels. The application rate for diflurobenzuron in the manure is also very low when compared with the normal crop application rates (up to 1.0 lbs ai/A). No detectable residues of diflubenzuron and/or its metabolites are expected in rotated crops as a result of using swine feed-through manure on cropland as a fertilizer, when applied in a manner to minimize N/P runoff.

Appendix A

Subject: Chemistry Science Advisory Council (ChemSAC) Meeting Minutes

Meeting Date: August 6, 2014

To: HED's Chemistry Interest Group

From: HED's ChemSAC

1. Diflubenzuron Swine Feed-Through Issue (T. Morton)

Background

A registrant for diflubenzuron has petitioned for a swine feed-through use of diflubenzuron. In their submission they calculate the loading of diflubenzuron from application of manure to cropland as 0.10 lb ai/A. Currently tolerances exist for barley, wheat, cotton, soybean, crop group 5B, artichoke, rice, peanut, peppers, stone fruit, citrus fruit, and tree nuts. Crop group 5B and turnip green tolerances are 9.0 ppm. Wheat forage and hay tolerances are 7.0 ppm. The proposed application rate is 0.3 mg/kg/day for swine weighing less than 100 pounds and 0.2 mg/kg/day for swine weighing more than 100 pounds. A cattle feed-through use is currently registered but the registrant stated this use is mostly for range-pastured cattle. T. Morton requested ChemSAC review of this issue for guidance on whether residue data should be required. After lengthly discussion, it was determined a tiered approach for residue data should be requested.

ChemSAC Conclusion

The SAC concluded the registrant should dose three hogs at the proposed rate of the diflubenzuron feed-through product. The manure should be collected and processed in the same way as swine manure is regularly processed prior to field application (i.e. dried, pH adjustment, aged, etc). The manure should then be analyzed for diflubenzuron and its metabolites (PCA and CPU). If quantifiable residues of parent or metabolite are found, then a small-scale residue field trial program should be conducted on representative crops (including at least corn and radish). All RACs should be collected and analyzed for diflubenzuron, and its metabolites (PCA and CPU). If quantifiable residues are found in these commodities, then a larger-scale residue program may be required on additional RACs. It is recommended the registrant consult with the Agency after the manure is analyzed to determine if the small-scale residue program is required.

Appendix B

MEMORANDUM

SUBJECT: Review of Diflubenzuron Residues in Swine Manure and Applied Crops

FROM: Don Atwood, PhD., Entomologist
Science and Information Analysis Branch
Biological and Economic Analysis Division (7503P)

THRU: Arnet Jones, Chief
Biological Analysis Branch
Biological and Economic Analysis Division (7503P)

TO: Deborah McCall, Chief
Invertebrate & Vertebrate Branch 2
Registration Division (7505P)

This memorandum transmits the review of the document "Diflubenzuron Residues in Swine Manure and applied Crops". As requested by the Registration Division, the review is limited to specific questions. BEAD was able to assess the accuracy of the calculations and state regulations and has provided additional usage information for swine manure on crops in the United States.

1. Can BEAD verify the calculations on pages 7-13 for both rates based on N level and P level allowed by regulations.

   The calculations appear accurate other than what is most likely rounding errors in the decimal positions. However, it appears that they must have assumed different lbs of plant available nitrogen and phosphorous for the Agitated H2O and Pond H2O in Table 3. As such I cannot verify the calculations for Lagoon Surface.

2. Can BEAD verify the state regulations the registrant lists within this study.

   The state regulations which were listed in this study were located and determined to be accurate.

3. Can BEAD provide a list of crops which they feel hog manure could be applied to.

   Overall, Manure was spread as fertilizer on about 15.8 million acres of U.S. cropland in 2006, just 5 percent of total planted acreage of 315.8 million acres. In principle, manure could be spread on far more cropland, mitigating the risks that arise from excessive concentrations of manure and replacing high-priced commercial fertilizers. But there are several barriers to wider use. Over half (52 percent) of harvested crop acres were on farms with no livestock production at all. Across crops, the share of harvested acreage on farms with no livestock varied from 80 percent for cotton and 70 percent for peanuts, to 51-62 percent for soybeans, corn, wheat, sorghum, and barley, to less than 30 percent for oats and hay. Farms that combine crop and livestock production are much more likely to spread manure on their cropland.

   The 2009 USDA report to Congress on "Manure Use for Fertilizer and Energy" indicates the crops receiving the most manure applications are corn (57.6%), soybeans (6.2%), cotton (2.5%), wheat (2.5%), and oats (2.4%). However, these numbers represent applications from all manure sources.

   There are really no limitations on which crops hog manure can be applied to. Recommended application sites include field crops, vegetable crops, and fruit crops. For liquid manure it is generally recommended that it be "applied and incorporated in fields where crops are intended for human consumption at least three months before the crop will be harvested. Allow four months between application and harvest of root and leaf crops that come in contact with the soil. Do not surface apply raw manure under orchard trees where fallen fruit will be harvested" (Minnesota Extension).

   However, the 2009 USDA report did indicate that hog producers spread manure on 244,000-516,000 acres of hay and grassland. Those who listed hay and grasses as the primary crop spread manure on 244,000 acres. Those who listed another primary crop spread manure on 2.21 million acres of the primary crop (90% was corn) and 272,000 acres of secondary crops. If all of those secondary acres were hay and grasses, then manured hay and grass acreage could have been as high as 516,000 acres. No other crops were identified in the report. Although use on numerous crops cannot be ruled out, corn is by far the largest crop receiving hog manure application.